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Comparison of the usefulness of selected formulas for GFR estimation in patients with diagnosed chronic kidney disease

Porównanie użyteczności wybranych wzorów stosowanych do szacowania GFR wśród pacjentów z rozpoznaną przewlekłą chorobą nerek

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A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
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G Funds Collection

Summary

Introduction: The diagnosis and classification of chronic kidney disease (CKD) are based on the glomerular filtration rate value. The simplest way to evaluate glomerular filtration rate is to estimate it based on serum creatinine concentration using one of many specific mathematical formulas. None of the formulas created for this purpose are perfect. Differences in eGFR values are frequently observed in specific stages of chronic kidney disease by KDIGO classification based on different formulas.

Aim: The aim of the study is to compare the eGFR value in patients previously diagnosed with CKD treated in the Outpatient Nephrology Unit of the University Hospital in Krakow using the selected formulas.

Material/Methods: The study was performed in a group of 882 patients (392 women, 490 men) aged 65.0 ± 14.8 years. GFR values were estimated using Bjornsson, the abbreviated MDRD, and CKD-EPI formulas. These values were then compared according to chronic kidney disease stage and age groups: above and below 60 years.

Results: The mean eGFR value was for Bjornsson formula- 47.2 ± 21.1 ml/min/1.73m^2, abbreviated MDRD formula- 38.8 ± 15.2 ml/min/1.73m^2, and CKD-EPI formula- 37.7 ± 15.9 ml/min/1.73m^2. There was a large concordance in eGFR values obtained using the CKD-EPI and abbreviated MDRD formulas in every stage of chronic kidney disease and in both age groups. The Bjornsson formula significantly increased the number of patients in early stages of CKD, G1 - 33 vs 2 (abbreviated MDRD) and 6 (CKD-EPI), G2- 186 vs 70 (abbreviated MDRD) and 69 (CKD-EPI).

Conclusions: CKD-EPI and abbreviated MDRD formulas have a similar usefulness in GFR value estimation in patients with diagnosed chronic kidney disease. Lower eGFR values achieved using abbreviated MDRD formula and CKD-EPI equation in comparison with Bjornsson's formula may result in an increased number of patients diagnosed with CKD.

Keywords: **chronic kidney disease • Bjornsson formula • abbreviated MDRD formula • CKD-EPI equation**

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Introduction

Chronic kidney disease (CKD) patients are a large and important group of the Nephrology Outpatient Units patients. Evaluation of kidney function is an essential part of a proper medical examination. Kidneys play an important role in a water-electrolyte and acid-base balance; they participate in the process of excreting metabolic products as well as in the regulation of blood pressure. Early identification and management of CKD and nephroprotection may slow down the progression of renal damage and delay the initiation of renal replacement therapy (RRT). The expanse of MDRD (Modification of Diet in Renal Disease) formula in Poland for estimating glomerular filtration rate (eGFR) and the extensive training addressed to general practitioners and specialists have drawn attention to the scale of CKD problems from doctors and from patients. This resulted in a significant increase in the number of patients referred to Nephrology Outpatient Units due to decreased glomerular filtration rate [12,29]. However, it frequently happens that a patient with only a small decrease in GFR is referred to a nephrologist instead of being treated and supervised by a general practitioner. This may be due to the deficiency of GFR estimation formula alone or to the improper understanding of the nature of glomerular filtration. The GFR value defines kidney function and the degree of decline in kidney function in a conventional way, but it depends on many factors that should always be considered. These include age, gender, race and weight. Other interfering factors are: dietary habits, exercise, pregnancy, hyperglycaemia, antihypertensive drugs, acute and chronic kidney disease. Glomerular filtration rate value is expressed as the clearance of a substance in ml from which the blood is cleansed in the kidney during one minute. The substance cannot be secreted or absorbed by renal tubules or the gastrointestinal tract [44]. The most accurate method to calculate GFR, the gold standard, is to measure it by exogenously administered compounds: inulin (exogenous glucose polymer, used as one of the first, now sparsely due to its invasive nature) or radiolabelled compounds: 51Cr-EDTA (chromium-51 labelled ethylenediamine tetraacetic acid), 99mTc-DTPA (technetium-99 labeled diethylenetriamine pentaacetic acid), iothalamate, iohexol. However, these methods are costly, time-consuming and cumbersome for primary and outpatient nephrological care. These are mainly used in selected clinical situations such as the evaluation of a live kidney donor or for the verification of other methods [21,24]. In common practice creatinine clearance is used to assess GFR. Creatinine is produced by muscles and almost entirely excreted by the glomerulus. The increase of serum creatinine concentration is a result of kidney structure damage. However, due to the fact that it is observed after the loss of about half of active nephrons, it is not possible to assess properly the extent of renal tissue diminution [32]. For this reason, since the 1970s, mathematical formulas have been developed to estimate GFR with the use of several additional variables, such as body weight, height, age, race, gender and serum albumin. There are several dozen formulas for estimating glomerular filtration rate including: Bjornsson, Jellife 1 and 2, Mawer or Gates formulas [3,18,22]. The most popular and commonly used are: Cockcroft-Gault, 6-variables and abbreviated MDRD and CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equations [9,19,30,31]. In children population, Schwartz or Counahann-Barrat equations are used to estimate GFR [11,42]. The great number of formulas developed to estimate glomerular filtration rate means that neither one is perfect. There is still a need for an optimal method to achieve the most accurate evaluation of kidney function. According to the information available in literature, Cockcroft-Gault and Bjornsson's formula derived eGFR values are most similar measurements based on the iohexol calculation [4]. We performed a retrospective study to assess the prevalence of specific stages of chronic kidney disease in patients previously diagnosed with CKD treated in the Outpatient Nephrology Unit by estimating GFR using: Bjornsson's formula as well as commonly used abbreviated MDRD and CKD-EPI equations.

Material and methods

The study was performed retrospectively on a group of 882 patients (392 women, 490 men) treated in the Nephrology Outpatient Unit of the University Hospital in Krakow with previously diagnosed CKD. The mean age of the patients was 65.0 ± 14.8 years. Mean serum creatinine concentration in the study group was 1.93 mg/dl and all patients met the criteria for CKD diagnosis. Additional laboratory parameters are summarized in table 1. GFR values were estimated using Bjornsson's, abbrevia-

ted MDRD and CKD-EPI formulas as follows:

Bjornsson's formula:

$$\text{eGFR for men} = \frac{[27 - (0.173 \times \text{age})] \times \text{weight} \times 0.07}{\text{Scr}}$$

$$\text{eGFR for women} = \frac{[25 - (0.175 \times \text{age})] \times \text{weight} \times 0.07}{\text{Scr}}$$

Abbreviated MDRD formula:

$eGFR = 186 \times S_{cr}^{-1.154} \times age^{-0.203}$ (x 0.742 when woman) (x 1.212 when black race)

CKD-EPI formula for women:

$eGFR = 144 \times (Scr/0.7)^{-0.329} \times 0.993^{age}$ when Scr ≤ 0.7 mg/dl

$eGFR = 144 \times (Scr/0.7)^{-1.209} \times 0.993^{age}$ when Scr > 0.7 mg/dl

CKD-EPI formula for men:

$eGFR = 141 \times (Scr/0.9)^{-0.411} \times 0.993^{age}$ when Scr ≤ 0.9 mg/dl

$eGFR = 141 \times (Scr/0.9)^{-1.209} \times 0.993^{age}$ when Scr > 0.9 mg/dl

Results

We analyzed the eGFR of 882 patients. Most of them were over 60 years old (600, 68%). The mean eGFR in the study group was 47.2 ± 21.1 ml/min according to Bjornsson's formula, 38.8 ± 15.2 ml/min according to the abbreviated MDRD formula and 37.7 ± 15.9 ml/min according to the CKD-EPI equation. The distribution of individual eGFR values according to the used formula is shown in figures 1, 2 and 3. The mean eGFR values in the age groups over and under 60 years old, according to the used formula, are shown in table 2. The number of patients in consecutive stages of chronic kidney disease introduced by KDIGO 2012 [26], according to the used formula is displayed in table 3. According to the used formula, in the population under and over 60 years old, the comparison of patients in consecutive stages of CKD is presented in tables 4 and 5. The following data shows a large concordance of abbreviated MDRD and CKD--EPI equations in the estimation of the glomerular filtration rate in all stages of chronic kidney disease and in both age groups. According to Bjornsson's formula, the estimation of GFR significantly increases the number of patients in early stages of CKD, especially in the age group <60 years.

Discussion

Chronic kidney disease has become one of the major medical problems of our time. CKD is considered to be a civilization disease. There is a steady global increase in the incidence of the disease. Literature data shows approximately 10% of the average incidence of CKD in the world's population [10]. Chronic kidney disease leads to the need for renal replacement therapy and from its early stages it is associated with an increased risk of morbidity, complications and mortality due to cardiovascular causes [7,14,17,36,41]. For these reasons, there is a need for early diagnosis of CKD which would make it possible, by appropriate preventive and curative procedures, to delay the disease progress and prevent

Table 1. Selected laboratory parameters in the study group

Parameter	Mean value ± SD	Normal laboratory values
Age (years)	65.0 ± 14.8	NA
Gender, male/female (%)	490/392 (55.5/44.5)	NA
BMI	27.4 ± 4.8 kg/m^2	18.5 - 25 kg/m^2
Creatinine	1.93 ± 0.9 mg/dl	0.5-1.1 mg/dl
Urea	11.4 ± 5.0 mmol/l	1.7-8.3 mmol/l
Hemoglobin	13.03 ± 1.8 g/dl	11-17 g/dl
Calcium	2.32 ± 0.18 mmol/l	2.02-2.61 mmol/l
Phosphates	1.24 ± 0.37 mmol/l	0.87-1.45 mmol/l
Natrium	139.1 ± 10.4 mmol/l	138-147 mmol/l
Potassium	4.6 ± 0.6 mmol/l	3.5-5.5 mmol/l
PTH (intact)	187.7 ± 242.6 pg/ml	12-65 pg/ml
Iron	15.7 ± 10.4 µmol/l	10.6-28.3 µmol/l
Magnesium	1.04 ± 1.69 mmol/l	0.7-1.05 mmol/l
Total protein	69.1 ± 9.6 g/l	60-80 g/l
Albumin	40.0 ± 6.5 g/l	35-50 g/l
Uric acid	402.2 ± 109.9 µmol/l	202-416 µmol/l
Total cholesterol	5.45 ± 1.32 mmol/l	3.2-5.2 mmol/l

Table 2. Mean values of eGFR in the study group according to the formula used

eGFR (ml/min/1,73m^2)	Bjornsson's (A) n = 882	Abbreviated MDRD (B) n = 882	CKD-EPI (C) n = 882	Differences between formulas
Mean value ± SD	47.2 ± 21.1	38.8 ± 15.2	37.7 ± 15.9	A-B= 8.4 A-C= 9.5 B-C= 1.1
Age <60 years (n =282)	57.0 ± 24.3	41.7 ± 17.9	42.9 ± 19.2	A-B= 15.3 A-C= 14.1 B-C= -1.2
Age >60 years (n = 600)	42.6 ± 17.5	37.4 ± 13.5	35.3 ± 13.4	A-B= 5.2 A-C= 7.3 B-C= 2.1

Table 3. CKD stages according to the formula used

CKD stage	Bjornsson's				Abbreviated MDRD				CKD-EPI			
	Total n= 882 n (%)	<60yo 282 (32%) n (%)	>60yo 600 (68%) n (%)	p (χ^2)	Total n= 882 n(%)	<60yo 282 (32%) n (%)	>60yo 600 (68%) n (%)	p (χ^2)	Total n= 882 n (%)	<60yo 282 (32%) n (%)	>60yo 600 (68%) n (%)	p (χ^2)
G1	33 (3.7)	27 (9.6)	6 (1)	<0.00001	2 (0.2)	2 (0.7)	0 (0)	<0.00001	6 (0.7)	6 (2.1)	0 (0)	<0.00001
G2	186 (21.1)	95 (16.3)	91 (15.2)		70 (7.9)	40 (14.2)	30 (5)		69 (7.8)	45 (15.9)	24 (4)	
G3a	217 (24.6)	68 (24.1)	149 (24.8)		214 (24.2)	79 (28)	135 (22.5)		194 (22)	77 (27.3)	117 (19.5)	
G3b	246 (27.9)	56 (19.8)	190 (31.6)		343 (38.9)	88 (31.2)	255 (42.5)		329 (37.3)	84 (29.8)	226 (37.6)	
G4	179 (20.3)	27 (9.6)	152 (25.3)		209 (23.7)	52 (18.4)	157 (26.2)		234 (26.5)	50 (17.7)	203 (33.8)	
G5	21 (2.3)	9 (3.2)	12 (2)		44 (5)	21 (7.4)	23 (3.8)		50 (5.7)	20 (7.1)	30 (5)	

complications. Chen et al. described a slower decline in glomerular filtration rate in patients who were referred early to a nephrologist. This was due to a better control of blood pressure, glycaemia, more frequent intake of angiotensin converting enzyme inhibitors and less frequent intake of nonsteroidal anti-inflammatory drugs [5]. Significantly better survival and a reduction in an annual decline of GFR value from 5.4 ml/min/1.73m^2 to 0.35 ml/min/1.73m^2 were reported by Jones et al. in patients referred to a nephrologist. This was seen especially during the first year after referral [23]. The classification of chronic kidney disease is based on the KDIGO (Kidney Disease Improving Global Outcomes) guidelines, which in 2012 proposed a new version. There are currently 5 stages of CKD (G1-G5) depending on the glomerular filtration rate value. Stage G3 is now subdivided into G3a and G3b [26]. GFR estimating methods are constantly under discussion. Choosing the right method to estimate glomerular filtration rate is of great importance, especially in ethnic groups and elderly patients [23,25,34,45,46]. The physiological decline of glomerular filtration with age may, with an imprecise formula or improper knowledge of the nature of glomerular filtration, lead to an over-diagnosis of chronic kidney disease, especially in elderly patients [37]. In the initial assessment to estimate GFR, the KDIGO guidelines recommend using the CKD-EPI equation based on serum creatinine concentration [26]. Due to its simplicity, an abbreviated MDRD formula is still widely used. The Cockcroft-Gault formula is also frequently used and may be useful especially in the evaluation of drug doses due to a lack of reference to the body surface [27]. In

Table 4. Comparison of the consecutive stages of CKD according to the formula used in patients <60 years old

CKD stage	Age <60yo n= 282 (32 %)								
	MDRD n (%)	CKD-EPI n (%)	p (χ^2)	MDRD n (%)	Bjornsson's n (%)	p (χ^2)	CKD-EPI n (%)	Bjornsson's n (%)	p (χ^2)
G1	2 (0.7)	6 (2.1)	0.78	2 (0.7)	27 (9.6)	<0.00001	6 (2.1)	27 (9.6)	<0.00001
G2	40 (14.2)	45 (15.9)		40 (14.2)	96 (33.9)		45 (15.9)	96 (33.9)	
G3a	79 (28)	77 (27.3)		79 (28)	68 (24.1)		77 (27.3)	68 (24.1)	
G3b	88 (31.2)	84 (29.8)		88 (31.2)	56 (19.8)		84 (29.8)	56 (19.8)	
G4	52 (18.4)	50 (17.7)		52 (18.4)	27 (9.6)		50 (17.7)	27 (9.6)	
G5	21 (7.4)	20 (7.1)		21 (7.4)	9 (3.2)		20 (7.1)	9 (3.2)	

Table 5. Comparison of the consecutive stages of CKD according to the formula used in patients > 60 years old

CKD stage	Age >60yo n= 600 (68%)								
	MDRD n (%)	CKD-EPI n (%)	p (χ^2)	MDRD n (%)	Bjornsson's n (%)	p (χ^2)	CKD-EPI n (%)	Bjornsson's n (%)	p (χ^2)
G1	0 (0)	0 (0)	0,06	0 (0)	6 (1)	<0,00001	0 (0)	6 (1)	<0.00001
G2	30 (5)	24 (4)		30 (5)	91 (15.2)		24 (4)	91 (15.2)	
G3a	135 (22.5)	117 (19.5)		135 (22.5)	149 (24.8)		117 (19.5)	149 (24.8)	
G3b	255 (42.5)	226 (37.6)		255 (42.5)	190 (31.6)		226 (37.6)	190 (31.6)	
G4	157 (26.2)	203 (33.8)		157 (26.2)	152 (25.3)		203 (33.8)	152 (25.3)	
G5	23 (3.8)	30 (5)		23 (3.8)	12 (2)		30 (5)	12 (2)	

our study we decided to analyze Bjornsson's formula, one of the less commonly used formulas for GFR estimation, which was developed in the late 1970s and, except serum creatinine concentration for estimating GFR, it requires age, gender and weight. The formula was chosen for the comparison, as it was suggested by the literature that it might give eGFR values similar to measured GFR. Bjornsson's formula calculation gave significantly higher eGFR values in our study group compared to abbreviated MDRD and CKD-EPI equations: the mean eGFR was 8.4 ml/min/1.73m^2 higher than achieved using the MDRD formula (47.7 vs. 38.8) and 9.5 ml/min/1.73m^2 higher than given by CKD-EPI equation (47.2 vs. 37.7). The differences were noticed in both age groups and expressed more in patients under 60 years old (mean eGFR 15.3 ml/min/1.73m^2 higher than given by abbreviated MDRD formula and 14.1 ml/min/1.73m^2 higher than given by CKD-EPI equation). The mean eGFR in patients older than 60 years old was approximately 6.2 ml/min/1.73m^2 higher for Bjornsson's formula than for the other two equations (Tab. 2). Lower eGFR values achieved using abbreviated MDRD formula and CKD--EPI equation naturally resulted in an increased number of patients in higher stages of CKD, especially over G3b stage with two times more patients in G5 CKD stage (MDRD- 44 patients, CKD-EPI- 50 patients, Bjornosson's formula- 21 patients). Use of MDRD and CKD-EPI formulas in some cases might result in over-diagnosis of

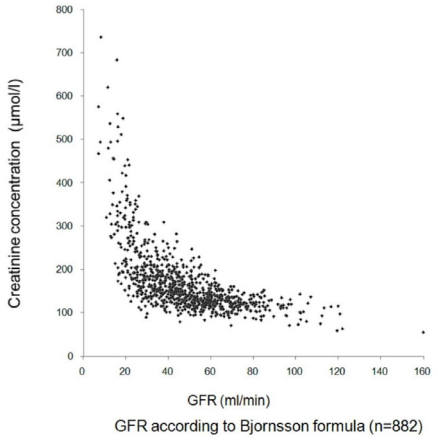

Fig. 1. Relationship between serum creatinine concentrations and eGFR values according to Bjornsson's formula

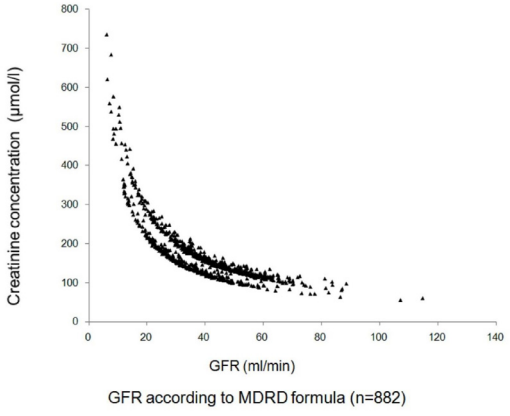

Fig. 2. Relationship between serum creatinine concentrations and eGFR values according to the abbreviated MDRD formula

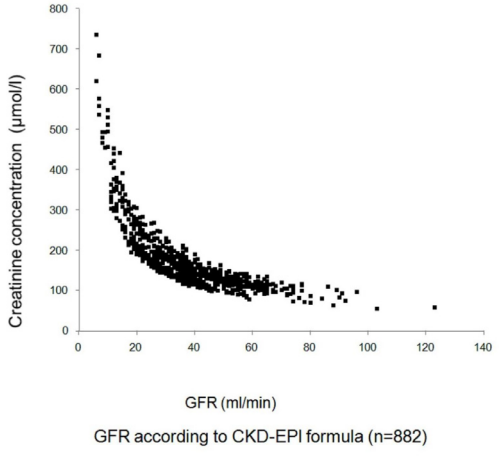

Fig. 3. Relationship between serum creatinine concentrations and eGFR value according to the CKD-EPI formula

higher stages of the disease as compare with Bjornsson's formula. Rocco et al. after analyzing the data of 9,308 patients found that the abbreviated MDRD formula led to an increase in the number of patients in the 3rd and 4th stages of CKD as compared with CKD EPI [40]. Chowdhury et al. noted that in elderly patients with hypertension, the MDRD formula underestimates GFR in lower stages of CKD but did not have any impact on the all--cause and cardiovascular mortality of these patients [7]. The underestimation of glomerular filtration rate according to the MDRD formula in higher GFR values can be found in other studies [6,8,16,35]. On the other hand, it is also described that Bjornsson's formula tends to overestimate glomerular filtration rate, especially in patients with lower GFR value. Such a conclusion can be found in Raj's et al. study in renal transplant patients. It is worth noticing that Bjornsson's formula showed the least bias in GFR estimation in patients with mGFR (measured GFR)> 50 ml/min [39]. Higher accuracy of this equation but also only in early CKD stages patients after analyzing the eGFR according to eight available equations: Cockcroft-Gault, 6-variables and abbreviated MDRD, Bjornsson, Jellife 1, Jellife 2, Mawer and Gates were reported in other studies [2,4]. It is not possible to unequivocally state which calculation in our comparison is the most similar to the real glomerular filtration value, which is the defect of the study. The best method to get the answer could be by comparing the formulas to mGFR (e.g. measured using iohexol). In our study, GFR estimation using abbreviated MDRD and CKD-EPI formula gave very similar results. The high similarity was observed not only in the mean eGFR (MDRD- 38.8 ml/min/1.73m^2, CKD-EPI- 37.7 ml/min/1.73m^2), but in both age groups and in every stage of the disease as well. The comparison of MDRD and CKD-EPI equation is the subject of the largest number of studies on GFR estimation [13,33,38,43]. Lower accuracy of the MDRD formula in comparison to CKD-EPI equation based on serum creatinine concentration in older patients with glomerular filtration rate > 60 ml/min was reported inter alia by Kilbride et al. [28]. Nonetheless, in the population of patients with moderate and severe kidney damage, both of the equations appear to have a similar value. In a large group of 38188 patients, Giavarina et al. reported a significant correlation of the formulas in estimating GFR, when it is lower than 60 ml/min/1.73m^2 [20]. Al-Magbali et al. compared CKD-EPI equation, 6-variables and abbreviated MDRD formula in 607 patients with diabetes and noted a high correlation between abbreviated MDRD and CKD-EPI formulas in G3 stage of CKD. They recommend using the abbreviated rather than 6-variables MDRD formula [1]. A similar accuracy of the abbreviated MDRD formula and CKD-EPI equation when mGFR is < 60 ml/min/1.73m^2 was also observed in older patients (mean age 80 years) [28]. However, according to Earley et al., none of the two formulas are adequate to estimate glomerular filtration rate for the full range of values [15]. Nevertheless, given the good correlation between the two formulas, the benefits of using the CKD-EPI equation in patients

with diagnosed chronic kidney disease are minor and the accuracy of the abbreviated MDRD formula remains sufficient enough to allow for the assessment and management of such patients [13,38].

In summary we can state that the CKD-EPI equation and abbreviated MDRD formula have a similar value in estimating glomerular filtration rate in patients with higher stages of chronic kidney disease. Lower eGFR values achieved using abbreviated MDRD formula and CKD--EPI equation in comparison with Bjornsson's formula may result in an increased number of patients diagnosed with CKD.

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